REMARKS

Claims 1-11 are pending in the current application. In an Office Action dated November 6, 2006 ("Office Action"), the Examiner rejected claims 4 and 6 under 35 U.S.C. § 112, second paragraph, as being indefinite, rejected claims 1, 5, and 6 under 35 U.S.C. § 102(b) as being anticipated by Empedocles et al., U.S. Patent Application Publication No. 2002/0028457 ("Empedocles"), rejected claims 1-3, 5-6 under 35 U.S.C. § 102(b) as being anticipated by Yakhini et al., EP 1162572 ("Yakhini"), rejected claims 1, 3, and 5-11 under 35 U.S.C. § 102(b) as being anticipated by Lockhart et al., U.S. Patent No. 6,344,316 ("Lockhart"), rejected claims 1-3 and 5-11 under 35 U.S.C. § 103(a) as being unpatentable over Rothberg et al., U.S. Patent No. 6,355,423 ("Rothberg") in view of Lockhart, and rejected claim 4 under 35 U.S.C. § 103(a) as being unpatentable over Rothberg in view of Lockhart and further in view of Walt et al., U.S. Patent No. 6,327,410 ("Walt"). Applicants have amended the claims to address certain of the Examiner's 35 U.S.C. § 112, second paragraph, rejections as well as to more particularly point out that which Applicants regard as their invention. Applicants respectfully traverse the above-listed rejections based on 35 U.S.C. § 102(b) and 35 U.S.C. § 103(a) and certain of the rejections based on 35 U.S.C. § 112, second paragraph.

Positive and Negative Control Features, Reference Patterns, and Pattern Blocks

In reviewing the rejections and the cited references, it appears to Applicants that the Examiner has failed to understand the meaning of various claim terms and phrases. In the following paragraphs, Applicants' representative discusses the meanings of certain terms and phrases of claim 1. First, the phrases "positive control feature" and "negative control feature" are discussed, on lines 27-30 of page 8:

> Positive control features are designed to generate high-intensity signals following exposure of the microarray to a sample solution, and negative control features are designed to generate no signal or a low intensity signal.

These phrases are also well-known to designers, manufacturers, and users of microarrays.

A control feature is not a probe feature, that is designed to reflect the presence or absence, or, in certain cases, the concentration of, particular target molecules in solutions to which a microarray are exposed. Instead, a positive control feature is designed to always produce a high signal, regardless of the particular sample solution to which a microarray is intended to be exposed, and a negative control feature is designed to produce either no signal or only a very low signal, regardless of the particular sample solution to which a microarray is intended to be exposed. That is why these features are called "control features." A control in an experiment is something that is known beforehand to produce a deterministic result.

Second, the phrase "pattern block" is defined multiple times, and consistently, in the current application. For example, beginning on line 30 of page 8, the current application states:

> The embedded calibration device comprises a set of pattern blocks, each pattern block comprising a number of microarray features arranged in a specific pattern of low-intensity and high-intensity features, which are positioned at known locations on the microarray.

In claim 1, a pattern block is described as:

> each pattern block comprising positive and negative control features and including an arrangement of one or more nearest-neighbor, positive-control features around a central feature.

Thus, a pattern block is a distinct arrangement of positive and negative control features that produces a recognizable pattern of low and high intensity signals. Example pattern blocks are shown in Figures 16A and 16B, including pattern block 1608 outlined in Figure 16A by solid lines.

Third, a reference pattern is a set of pattern blocks, as stated on lines 16 - 18 of page 6 of the current application:

> The embedded control features comprise an array of pattern blocks, or a reference pattern, in which each pattern block is composed of a set of microarray features arranged in a specific pattern of low-intensity and high-intensity features.

A reference pattern thus consists of multiple pattern blocks. Figures 16A-B of the current application illustrate a representative reference pattern, described beginning on line 20 of page 18 of the current application as follows:

Figures 16A-B illustrate the design for a two-dimensional reference pattern or image. Figure 16A shows a two-dimensional reference pattern 1602 positioned in the upper left-hand corner of a hypothetical microarray 1603. The two-dimensional reference pattern 1602 comprises a 6 x 6 pattern-block matrix, indexed by rows (0-5) 1604 and by columns (0-5) 1606. The reference pattern shown in Figure 16 comprises 32 pixel-based pattern blocks, each rectangular pattern block, such as rectangular pattern block (0,0) 1608, comprising 25 hexagonally packed features. The two-dimensional reference pattern collectively represents all of the different possible arrangements of high-intensity and low-intensity nearest neighbor features about a central feature. Pattern blocks (2,4), (2,5), (5,4), and (5, 5) are not used, since there are only 32 possible nearest-neighbor arrangements, while there are 36 possible pattern blocks within the 6 x 6 pattern-block matrix. The pattern blocks are separated by rows and columns of low-intensity features to facilitate pattern-block recognition, and may facilitate automated methods that employ the two-dimensional reference pattern. In alternative embodiments, all 36 possible pattern blocks may be used by incorporation of redundant patterns.

Figure 16B provides a pattern-block-centric representation of Figure 16A. In Figure 16B, unfilled circles, such as unfilled circle 1610, represent central, low intensity features. In Figure 16B, the central feature of each pattern block is shown circumscribed by a dashed circle, such as dashed circle 1610. In the two-dimensional reference pattern, each pattern block in rows 0, 1, and 2 includes a high-intensity central feature, and each pattern block in rows 3, 4, and 5 includes a low-intensity central feature. Rows 0, 1, and 2 include pattern blocks representing all possible high and low-intensity feature patterns of the four nearest neighbors of a high-intensity central feature, and rows 3, 4, and 5 include pattern blocks representing all possible high and low-intensity feature patterns of the four nearest neighbors of a low-intensity central feature. For example, pattern blocks (0, 1), (0, 2), (0, 3), and (0, 4) include all possible arrangements of two high-intensity, nearest neighbor features about a high-intensity central feature.

Claim 1 recites:

1. A microarray comprising:

a substrate;

a number of features comprising probe molecules, each feature located at a different position on a surface of the substrate; and

at least one *reference pattern* that comprises *a number of pattern blocks*, each *pattern block comprising positive and negative control features and including an arrangement of one or more nearest-neighbor, positive-control features around a central feature*, a comparison of computed positions for

> reference-pattern features to reference-pattern feature positions, following scanning of the microarray, indicating a feature extractability problem. (emphasis added)

In other words, to anticipate claim 1, a microarray needs to contain a set of pattern blocks that together comprise a reference pattern. Each pattern block needs to comprise negative and positive control features that should, upon exposure and processing, produce a recognizable pattern of low and high intensity signals. The negative and positive control features are arranged in the pattern block so that a central control feature is surrounded by one or more positive control features, as in the pattern blocks shown in Figures 16A-B.

Traversal of the Claim Rejections

The Examiner rejects claim 6 as being indefinite for reciting a reference pattern position at multiple locations on a microarray. However, on lines 19-20 of page 6, the current application states:

> The reference pattern can be embedded or replicated anywhere on the surface of a microarray.

Please also note that claim 1 recites at least one reference pattern, and not a single reference pattern. Applicants' representative can see nothing indefinite or unclear about claim 6.

Applicants' representative has carefully read the cited portions of Empedocles, Yakhini, Lockhart, Rothberg, and Walt, and can find no teaching, mention, or suggestion of reference patterns comprising a set of pattern blocks, each pattern block, in turn, comprising arrangements of positive and negative control features. In particular, there is no teaching, mention, or suggestion of a microarray containing reference patterns comprising a set of pattern blocks, each pattern block, in turn, comprising arrangements of positive and negative control features.

In the cited portion of Empedocles, paragraph 108 and Figure 8, Empedocles discusses inclusion of alignment spots that are essentially positive control features to an array. There is no mention of negative control features. Figure 8 of

Empedocles shows 3 alignment spots surrounding a probe, and not surrounding a control feature. Thus, Empedocles fails to teach, mention, or suggest a pattern block comprising both negative and positive control features, and fails to teach, mention, or suggest a reference pattern comprising sets of pattern blocks.

Yakhini is directed to extraction of microarray data from a microarray. Figure 31 of Yakhini "illustrates a number of local backgrounds" of probe features. Paragraph [0067] of Yakhini is directed to determination of background intensities for each signal read from a microarray, and has nothing to do with pattern blocks or reference patterns, as clearly defined in the current application and discussed above. Paragraph [0067] does mention negative control features, but they are not mentioned as being included, together with positive control features, in a reference pattern or pattern blocks of a reference pattern. Applicant's representative is quite familiar with this application, having written it a number of years ago.

The cited portion of Lockhart discusses perfect-match and mismatch probes that are included in a microarray. A mismatch probe is complementary to the perfect match probe - and has a somewhat different sequence than that of the perfect-match probe. As explicitly stated by Lockhart, on lines 1-3 of column 9, in preferred embodiments, the mismatch probe differs from the perfect-match probe only in the identity of a single, central nucleotide. The perfect-match probe is a probe, and not a positive-control feature. It is designed to be complementary to a particular target sequence, like all microarray probe features, but is not designed to produce a high signal regardless of the sample solution to which the array is exposed. The mismatch probe is not a negative control probe. It generally binds to the same target molecule as the perfect-match probe, but with less affinity and specificity. Moreover, Lockhart does not teach, mention, or suggest pattern blocks containing control probes or reference patterns comprising sets of pattern blocks. The cited portion of Lockhart is unrelated to the subject matter to which claim 1 is directed.

The cited portions of Rothberg do not teach, mention, or suggest anything related to control features, pattern blocks, or reference patterns. Instead, Figure 5A of Rothberg illustrates a 256-probe array that includes probes and error-checking cells. The

error-checking cells "contain hybridization regions fully degenerate on one or more nucleotides ... to which a target nucleic acid should hybridize if it also hybridizes to a cell in the primary observation array with probes having a unique hybridization region sequence" (Rothberg, lines 13-18 of column 51). Thus, nothing in the 256-probe array illustrated in Figure 5A of Rothberg or discussed in the cited portion of Rothberg has anything to do with control features, pattern blocks comprising arrangements of negative and positive control features, or reference patterns. The cited portion of Rothberg is unrelated to the subject matter to which claim 1 is directed.

Finally, Walt is cited apparently for hexagonal arrangement of features. Walt discusses microwells for holding microbeads, rather than microarrays with features, as carefully and fully described in the current application. Moreover, Walt does not teach, mention, or suggest control features, pattern blocks, or reference patterns.

In summary, none of the cited references teaches, mentions, or suggests pattern blocks comprising both negative and positive control features, or reference patterns comprising a set of pattern blocks. None of the cited portions of the references teach, mention, or suggest both negative and positive controls within a microarray. Therefore, none of the references can anticipate claim 1, or the remaining claims of the current application that depend from claim 1. No combination of two or more of the cited references teach pattern blocks comprising both negative and positive control features, or reference patterns comprising a set of pattern blocks, and thus no combination of two or more of the cited references can make obvious claim 1, or the remaining claims of the current application that depend from claim 1.

In Applicant's representative's opinion, all of the claims remaining in the current application are clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,
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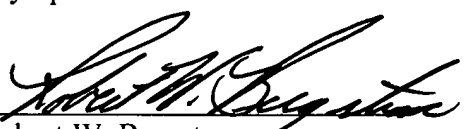

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